

Amendments to the Claims:

1-20. (Canceled).

21. (New) A method of changing a functional surface binding specificity of a PAS domain, wherein the PAS domain is predetermined, prefolded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity, the method comprising the steps of:

introducing into the hydrophobic core of the PAS domain a foreign ligand of the PAS domain; and

detecting a resultant change in the functional surface binding specificity of the PAS domain,

wherein the PAS domain is HIF2a PAS B, and the binding specificity is a change in intramolecular binding affinity of the PAS domain, detected as a change in chemical shifts detected by $^1\text{H}/^{15}\text{N}$ -HSQC NMR.

22. (New) A method of changing a functional surface binding specificity of a PAS domain, wherein the PAS domain is predetermined, prefolded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity, the method comprising the steps of:

introducing into the hydrophobic core of the PAS domain a foreign ligand of the PAS domain; and

detecting a resultant change in the functional surface binding specificity of the PAS domain,

wherein the PAS domain is HIF2a PAS B and is present as part of HIF2a, and the binding specificity is a change in intermolecular binding affinity of the PAS domain detected as a change in transcription complex formation of DNA: the HIF-2a:ARNT.